Microbiomes: I contain multitudes

Jesse Brunner

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> Do I contradict myself? Very well then I contradict myself, (I am large, I contain multitudes.) — Walt Whitman, Song of Myself]

The human as an ecosystem

From the origins of germ theory until quite recently our view of microbes was largely a negative one. They were parasites, decomposers, necessary but rather unwelcome members of the tree of life. As for their place in or on us? Well, we could tolerate them so long as they did not do too much harm, but we would probably be better off if we washed more thoroughly! It is thus pretty remarkable, at least to me, how much our view on microbes has changed in the last few decades. We now recognize that microbial life—Bacteria, Archaea, fungi, even protists and protozoa—is much, much more diverse and much, much more common than we'd previously recognized.

We also know that much of what we, as humans, are is microbial. Estimates are converging on about 1.3 (range of 1 – 3) bacterial cells in or on our body per human cell in healthy adults[1], not to mention the various fungi and viruses you or I harbor. Each of us is, in a very real sense[2], more symbionts than host; more bacterial than eukaryotic! And it is not just that there is "me," a body of comprised of eukaryotic cells derived from sperm and egg, with a thin veneer of an admittedly large number of symbiotic hangers on. No, as we shall see, the "me" I think about is very much the product of the interactions between my eukaryotic cells and my symbiotic partners. *I* am really *we*[3].

The human as a diversity hotspot

In addition to sheer numbers, we harbor an awful lot of microbial *diversity*, too, on our skin, in our guts, in our mouths, and so on. How many species? It turns out that is a tricky question to answer clearly, in part because of how we detect and measure this diversity. The vast majority of bacteria are not culturable; we only know of them through their genetic sequences. In rough outline samples from the skin or gut or whatever are collected, all of the DNA extracted, and then short sequences of random bits of DNA from the sample are then sequenced. Computer algorithms are then used to compare these sequences to each other to find overlapping regions and make longer sequences, which are then compared to databases of sequences, and run through yet other algorithms to estimate the number of species (or sometimes gene families or metabolic pathways). So the question of how many species depends on how much sampling you've done (although there are ways of estimating the whole sample from a part), the methods you used, and how you define a species.

[1] You might have heard estimates of 10 to 1, but apparently these were based on early back-of-the envelope calculations. Gilbert et al. 2018. Current understanding of the human microbiome. Nature Medicine 24:392-400..

[2] At least by cell number. Our eukaryotic cells are larger and thus make up more biomass than our microbial partners.

[3] There is far too much to even briefly mention. So instead let me point you to the terrific book by Ed Yong on the microbiome with a title riffing on Whitman's poem, *I Contain Multitudes: The Microbes Within Us and a Grander View of Life*.

Anyway, rough estimates are on the order 500 to 1000 bacterial species per person[4]. That is a lot of diversity, but it actually pretty conservative. There is enough genetic diversity in these samples to suggest something on the order of 20 – 50 subspecies or strains per bacterial species[5]. What's more, one recent analysis of some 3,655 samples found over 45,000,000 "non-redundant" genes, *half* of which were only found once! It is a staggering amount of genetic diversity in humans[6].

We have only begun to grasp this diversity in the last decade or so; the Human Microbiome Project, for instance, published its initial results in 2012. What is becoming clear is that while there are some commonalities, the microbiomes of different people can be quite different, and even the microbiome of an individual can change quite a lot over time. The microbial community even changes dramatically between different parts of the body!

[4] See Gilbert et al. 2018.

[5] Tierney et al. 2019. The Landscape of Genetic Content in the Gut and Oral Human Microbiome. Cell Host Microbe 26:283-295.e8

[6] Moreover, most samples come from American and Western European people; there is much more diversity to be found!

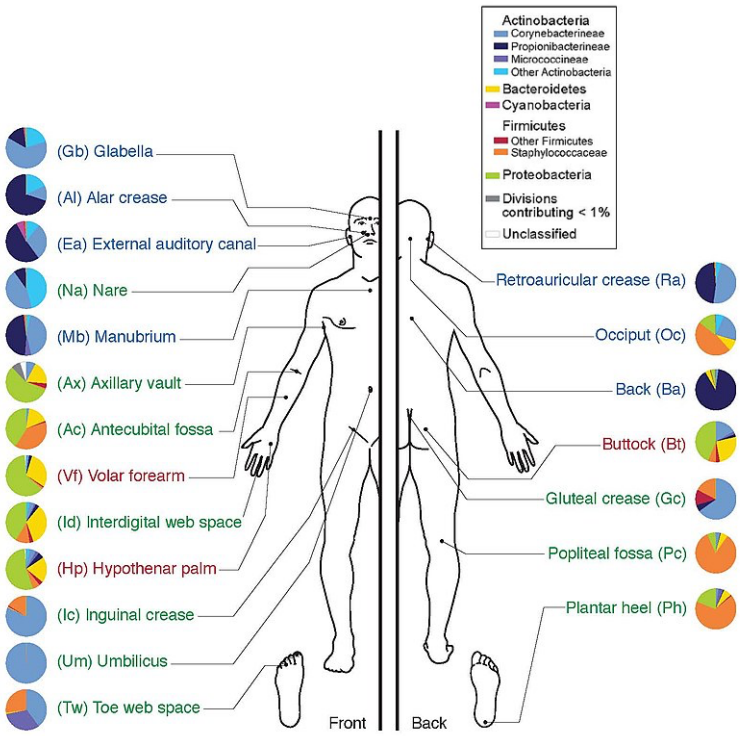

Figure 1: Major suborders of bacteria (colors) found on different parts the skin of a human. Illustration by Darryl Leja for the National Human Genome Research Institute (www.genome.gov).

The human as a rainforest, or how do we end up hosting such amazing diversity?

Important to note that an animal is, from the point of view of a microbe, a very large, very heterogeneous place. Our microbiomes are less the Petri dish you might think of when you think of microbes and much more a rainforest with all the nooks and crannies that calls to mind. At a course scale, the skin is quite different from the mouth is different from the gut, but the skin on the forearm is pretty different than that on the toe or armpit or groin. The upper part of the GI is

different from the lower end, the bends are probably different from the straight bits. Even within the mouth, the front of the mouth is pretty different from the back, the outside of the teeth from the parts between (which you really should be reaching with floss!). When I say different, I mean different temperatures, pH, oxygen availability, physical stability, nutrient availability, neighbors and more. In other words, what may at first seem like a fairly homogeneous environment (e.g., your gastrointestinal tract) actually offers a diversity of habitats.

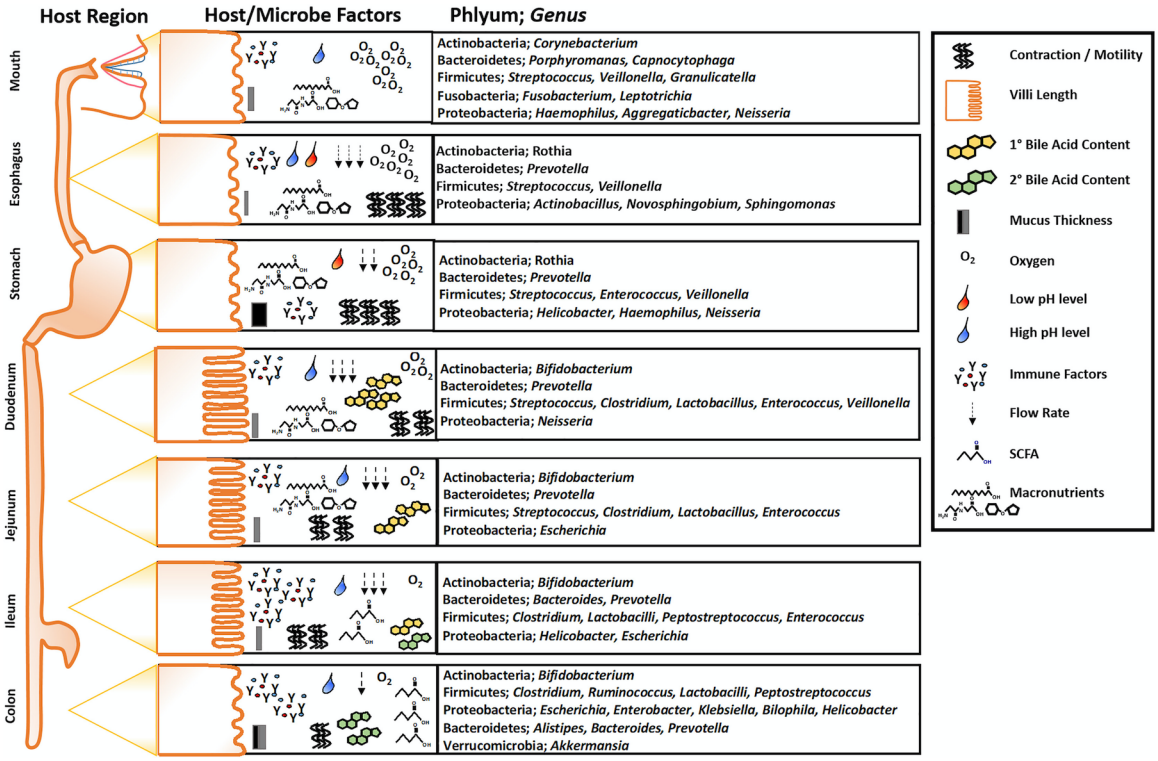

Figure 2: A tour of host conditions and representative members of the microbial community throughout the gastrointestinal tract. From [Martinez-Guryn et al. 2019 Regional Diversity of the Gastrointestinal Microbiome. Cell Host Microbe 26:314-324](https://pubmed.ncbi.nlm.nih.gov/31513770)

This variation in habitat is mirrored by variation in microbial species. After all, while some microbes can inhabit a wide range of conditions and use a variety of substrates as food, others can be very specialized (again, just like in a rainforest). A certain species may grow (or persist) best in one particular place, at least relative to others, and another might "prefer" another. This can result in what we call niche partitioning. The niche[7], as you've probably learned at some point in your past, can be defined as the suite of conditions and resources required for individuals of a species to survive, grow, and reproduce. Presumably[8] evolutionary processes often lead to species having different niches from one another (e.g., perhaps surviving at different temperatures, requiring different amounts of Fe and K, and so on), which leads to less competition between species.

Certainly there is some fine-scale matching between the niches of microbial species and the distinct nooks and crannies in and on us. But this alone cannot explain the tremendous diversity we observe. Again, this is an active area of research[9]. Still, we can think through this in the same way we might ask about the

[7] Well, there are actually many definitions of "niche". I am using Hutchinson's n-dimensional hyper volume, which is a way of thinking about a species' fundamental niche.

[8] I say presumably because this is very difficult to demonstrate.

[9] Meaning that we really do not know!

diversity in any community[10].

First, it is important to note that the microbes in and on us ultimately come from our environment, from the birth canal and our mothers's milk to all that dirt we eat and air we breath. But it is not as if *everything* we come across successfully colonizes. Our microbiome is a small, unique subset of bacteria in the broader world. That is, there is a great deal of selection against most bacteria we come across; most do not make the cut! Interestingly, if you change your, say, internal environmental conditions (e.g., become a vegetarian or get a GI infection), the composition of the microbiome changes somewhat in response. So know that only a subset microbes can actually be part of our microbiomes.

But focusing on those potential colonists, what controls whether they establish or not? Or in other words, how does our microbiome develop? Again, it's an act area of research, but let me offer three "models" of community assembly[11] that may help explain why we end up with the communities we do. I do not want to imply that this is exactly what is happening in our guts, but it does help illustrate the processes that may be at work, as well as how ecologists think through such a process.

1. Inhibition (or Preemption). This is a simple model that says that whatever arrives first prevents other things from taking that spot. As in, this stretch of the duodenum only has so many seats, and once species X is in that spot, it won't leave until it dies or some physical force removes it. Over time this sort of model suggests a shift from early colonists to a stable community of long-lived species.

2. Facilitation. You have undoubtedly run across this model. The first things to arrive somehow prepare the environment so that it better suits or facilitate the arrival of other species. Importantly, there is no intentionality here. The early arriving species do not set out to help others, but in doing what they do (e.g., maybe they end up leading to a thicker mucous layer) they somehow change the environment. This model, overall, suggests a specific sequence communities and the last, stable community is the one that does not change the environment.

3. Tolerance. This model, too, predicts a specific sequence of communities, but there is no facilitation. Rather, the idea is that later arriving species are better able to use limited resources or *tolerate* a deteriorating environment. Species persist until they can no longer function with whatever meager resources are left, and the community overall moves towards the toughest, most hard-scrabble species. (It's hard to imagine this is the case in the gut, where resources are constantly replenished, but maybe on the skin?)

Again, there could be elements of all three of these models at work, and probably other mechanisms, too. There are predators and parasites in this community, too. The environment is quite dynamics, too, diurnally, seasonally, and so on. Just like a rain forest! The point is not that we know how all of this works with

[10] Yes, it is very cool to think of ourselves as ecosystems, and we are, but we are not exactly unique as ecosystems. What applies to the Palouse or a rainforest applies equally well to us!

[11] First introduced by Connell & Slatyer in 1977 (Am Nat 111:1119-1144), these models still influence our thinking of community dynamics.

much certainty, but rather that the notion you may have of the community consisting of a variety of bacteria each of which fits nicely into its own little niche is…simplistic[12]. Every ecosystem is complex, whether it's a basin in a rainforest or us.

[12] OK, just plain wrong.